REMARKS/ARGUMENTS

This Amendment responds to the Official Action of September 24, 2007 and accompanies a Request for Continued Examination and an Information Disclosure Statement.

The claims have been amended to more particularly point out the inventive subject matter and direct them to further aspects of the disclosure.

Polynucleotides and polysaccharides have been added as options for the macromolecular principle, based on e.g. original claim 8 and the associated passages in the description. Please see the Annex A giving details experimental data prepared by the applicant as evidence of what was already explained in the application as filed (*see* e.g. page 3, lines 28-29, page 4, line 27 and page 6, line 24), namely that the macromolecular principle used in accordance with the present invention can be a polynucleotide or polysaccharide.

Independent claims 1 and 26 have been amended to specify that the compositions of the invention do not raise the pH above 7.5, based on page 7, lines 8-13.

New dependent claims 34 and 35 have been added, based on page 2, line 13, which further specify that the compositions do not raise the pH above 7.

The amendments filed June 1, 2007, namely the feature directed to compositions with an enteric coating which becomes permeable at a pH of from 3 to 7, have been revised, leading to the reinstatement of claim 3 (as new claim 31) and the introduction of new claim 32.

Dependent claim 33 has been added, based on page 1, lines 10-11 and 20-24 and page 2, lines 14-18, specifying that the enhancement of absorption of the macromolecular principles occurs due to the additive improving solubility of the bile salts.

Single, double and triple stranded RNA have been added to the list of macromolecular principles in claims 9 and 19, based on page 4, line 28.

Some corrections have been made to options (i) and (ii) in claims 1, 13, 14 and 26 and claims 13 and 14 have also been adjusted for consistency with claim 1.

It is believed that the issuance of the current Office Action has been caused by a misunderstanding as to what was agreed during the interview of May 17, 2007.

Response to Issues Raised in Official Action

In the response of June 1, 2007 the claims were amended, *inter alia*, to specify that the compositions of the invention are coated with an enteric coating which becomes permeable at a

pH of from 3 to 7. Other amendments were also made, to address objections under the categories "written description" and "enablement". However, this particular amendment was made specifically to address the Examiner's objection in the Office Action of February 1, 2007 that the claims were "obvious".

More specifically, it was thought that in the interview with the Examiner of May 17, 2007, all parties had agreed that making this particular amendment would result in a set of claims which are inventive, and (assuming certain other amendments were made too, which they duly were) allowable. The Examiner has since issued a further Office Action, maintaining that the amended claims also are "obvious". In view of this, it is believed that there may have been confusion between the particular amendment that (a) the Examiner, and (b) the applicant thought was required in order for inventiveness to be acknowledged.

Accordingly, the amendment of the claims to specify the enteric coating which becomes permeable at a pH of from 3 to 7 has been reversed, and the claims have been amended to specify instead that the composition, when introduced into the intestine, does not raise the pH of the intestinal fluid above pH 7.5. This new amendment is based on page 7 lines 8-13 of the application as filed.

For the reasons set out below, it is believed that this is the amendment the Examiner had accepted would enable her to acknowledge patentability for the present application.

Firstly, making this amendment should overcome the objection of obviousness which had originally been raised in the Office Action of February 1, 2007, and which was subject to discussion during the interview on May 17, 2007. More specifically, the chain of reasoning used by the Examiner in the objection of obviousness (which is repeated in the current Office Action) was as follows:

> "*It would have been obvious to one of ordinary skill in the art to substitute the propyl gallate for the sodium bicarbonate in the pharmaceutical composition... ...The skilled artisan would have been motivated to do so given that the pKa of propyl gallate is 8.11... ...and that New teaches that additives that buffer the gut between pH 7.5 and 9 increase the bioavailability of the insulin...*" (Point 13 of the current Office Action)

Thus, the skilled artisan would have been motivated (by New in US 5,853,748) to use additives that buffer the gut between pH 7.5 and 9. This means, he would have been led directly away from the compositions of the present invention, which, according to amended claim 1, specifically do not raise the pH of the intestinal fluid above pH 7.5. Therefore, the present invention simply cannot have been obvious in view of the cited prior art, because it is contrary to the direct teaching of that very same prior art.

Indeed, the present invention is based on the discovery of a mechanism of increasing the absorption of macromolecules which is not mentioned anywhere in the prior art cited by the Examiner. More specifically, the present invention concerns the enhancement of solubility of a non-conjugated bile acid or salt as a means of enhancing absorption of certain macromolecules. This is a completely different approach from that used in the prior art. This is explained in more detail at page 2 lines 3-22 of the application as filed. As noted there, the discovery that certain specific aromatics alcohols can improve the solubility of certain types of bile acids in certain pH conditions was unexpected, as it is simply not suggested anywhere in the prior art.

The Examiner has cited a further document (Alberts *et al*, Molecular Biology of the Cell) to support an assertion that the pH in the intestines is neutral. This is apparently in support of an argument that the enteric coatings mentioned in one of the prior art documents (US 5,853,748) would become permeable at pH 7. Thus, this point concerns the amendment that was filed as a consequence of the misunderstanding explained above. As that amendment has now been reversed, this point is no longer relevant to claim 1.

Moreover, this point has no bearing on the reasons set out above as to why the compositions of the present invention are inventive over the prior art. Indeed, the very same document that the Examiner is discussing at this point (US 5,853,748) is that which teaches readers to raise the pH above 7.5.

In view of the comments above and the amendments submitted herewith it is believed that the Examiner will now be able to acknowledge patentability for the present claims.

Respectfully submitted,

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ANNEX A

Example III(A) Preparation of chenodeoxycholate/propyl gallate mixture containing Poly-uridylic acid single-stranded RNA as macromolecular principal

1g of chenodeoxycholic acid is dissolved in 3.4g of sodium hydroxide solution (30mg/ml) with warming. The solution is brought to room temperature and adjusted to pH 7.85 by addition of further sodium hydroxide solution. 500mg of propyl gallate is then added and dissolved by shaking at room temperature to give a clear solution. The pH is adjusted to 7.45, frozen and lyophilised overnight to give a dry crystalline powder.

100mg of the powder is dissolved in 1ml of distilled water, and 500ul of the clear solution is added to 1mg of poly-uridylic acid single-stranded RNA and warmed in a water bath at 37 deg C. A clear solution is obtained after 5 minutes incubation. The solution is frozen and lyophilised overnight to give a dry crystalline powder once again. 500ul of phosphate buffered saline is added to the powder and warmed in a water bath at 37 deg C. A clear solution is obtained after 5 minutes incubation once again.

Example III(B) Preparation of chenodeoxycholate/propyl gallate mixture containing Polyuridylic acid – Polyadenylic acid double-stranded RNA as macromolecular principal

100mg of chenodeoxycholate/propyl gallate powder prepared as in Example III(A) is dissolved in 1ml of distilled water, and 500ul of the clear solution is added to 1mg of polyuridylic acid – polyadenylic acid double-stranded RNA and warmed in a water bath at 37 deg C. A clear solution is obtained after 5 minutes incubation. The solution is frozen and lyophilised overnight to give a dry crystalline powder once again. 500ul of phosphate buffered saline is added to the powder and warmed in a

water bath at 37 deg C. A clear solution is obtained after 5 minutes incubation once again.

Example III(C) Preparation of chenodeoxycholate/propyl gallate mixture containing Poly-cytidylic acid single-stranded RNA as macromolecular principal

A procedure identical to that described in example III(B) was performed, except that poly-cytidylic acid single-stranded RNA was employed instead of poly-uridylic acid single-stranded RNA, with identical results.

Example III(D) Preparation of chenodeoxycholate/propyl gallate mixture containing Poly-guanylic acid single-stranded RNA as macromolecular principal

A procedure identical to that described in example III(B) was performed, except that poly-guanylic acid single-stranded RNA was employed instead of poly-uridylic acid single-stranded RNA, with identical results.

Example III(E) Preparation of chenodeoxycholate/butylated hydroxy anisole mixture containing Polyuridylic acid single-stranded RNA as macromolecular principal

A procedure identical to that described in example III(A) was performed, except that butylate hydroxy anisole was employed instead of propyl gallate, with identical results.

Example III(F) Preparation of chenodeoxycholate/ butylated hydroxy anisole mixture containing Polyuridylic acid – Polyadenylic acid double-stranded RNA as macromolecular principal

A procedure identical to that described in example III(B) was performed, except that butylate hydroxy anisole was employed instead of propyl gallate, with identical results.

Example III(G) Preparation of chenodeoxycholate/ butylated hydroxy anisole mixture containing Poly-cytidylic acid single-stranded RNA as macromolecular principal

A procedure identical to that described in example III(C) was performed, except that butylate hydroxy anisole was employed instead of propyl gallate, with identical results.

Example III(H) Preparation of chenodeoxycholate/ butylated hydroxy anisole mixture containing Poly-guanylic acid single-stranded RNA as macromolecular principal

A procedure identical to that described in example III(D) was performed, except that butylate hydroxy anisole was employed instead of propyl gallate, with identical results.

Example III(I) Preparation of chenodeoxycholate/ butylated hydroxy anisole mixture containing Poly-adenylic acid single-stranded RNA as macromolecular principal

A procedure identical to that described in example III(H) was performed, except that poly-adenylic acid was employed instead of poly-guanylic acid, with identical results.

Example III(J) Preparation of chenodeoxycholate/sodium laurate mixture containing Poly-uridylic acid single-stranded RNA as macromolecular principal

A procedure identical to that described in example III(A) was performed, except that sodium laurate was employed instead of propyl gallate, with identical results.

Example III(K) Preparation of chenodeoxycholate/sodium caproate mixture containing Poly-uridylic acid single-stranded RNA as macromolecular principal

A procedure identical to that described in example III(A) was performed, except that sodium caproate was employed instead of propyl gallate, with identical results.

Example III(L) Preparation of chenodeoxycholate/sodium oleate mixture containing Poly-uridylic acid single-stranded RNA as macromolecular principal

A procedure identical to that described in example III(A) was performed, except that sodium oleate was employed instead of propyl gallate, with identical results.

Example III(M) Preparation of formulation containing Poly-uridylic acid single-stranded RNA, propyl gallate and sodium deoxycholate

Sodium deoxycholate in an amount of 750mg is mixed with 350mg of propyl gallate in a glass vial and 1.05ml of distilled water are added, to give a clear colourless solution on warming at 37 deg C. To 1mg of poly-uridylic acid single-stranded RNA 0.5ml of the deoxycholate/PG solution is added and incubated at 37 deg C. A clear solution is rapidly obtained. The contents of the vial are frozen rapidly with shaking and lyophilised overnight. The following day a dry solid is obtained. 500ul of phosphate buffered saline is added to the solid. A clear solution forms rapidly once again.

Example III(N) Preparation of formulation containing Polycytidylic acid single-stranded RNA, propyl gallate and sodium deoxycholate

A procedure identical to that described in example III(M) was performed, except that Polycytidylic single-stranded RNA was employed instead of poly-uridylic acid single-stranded RNA, with identical results.

Example III(O) Preparation of formulation containing Polyguanylic acid-single-stranded RNA, propyl gallate and sodium deoxycholate

A procedure identical to that described in example III(M) was performed, except that Polyguanylic single-stranded RNA was employed instead of poly-uridylic acid single-stranded RNA, with identical results.

Example III(P) Preparation of chenodeoxycholate/propyl gallate mixture containing Low-molecular weight heparin as macromolecular principal

A procedure identical to that described in example III(B) was performed, except that 20mg low-molecular weight heparin was employed instead of 1mg poly-uridylic acid single-stranded RNA, with identical results.

Example III(Q) Preparation of formulation containing Low-molecular weight heparin, propyl gallate and sodium deoxycholate

A procedure identical to that described in example III(M) was performed, except that 20mg low-molecular weight heparin was employed instead of 1mg poly-uridylic acid single-stranded RNA, with identical results.